

## Effect of pH on Sublingual Absorption of Oxycodone Hydrochloride

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### ABSTRACT

The purpose of this study was to develop a sublingual spray drug delivery formulation of oxycodone and evaluate the effect of formulation pH on sublingual absorption of oxycodone for acute pain management using rabbit as the animal model. Using a new, sensitive, and specific liquid chromatography/mass spectrometry (LC/MS) with electrospray ionization detector assay, the absorption bioavailability of sublingual oxycodone was determined in rabbits by comparing plasma concentration after sublingual spray delivery with equivalent intravenous dose. The effect of formulation pH on sublingual absorption of oxycodone was also tested on rabbits that had received oxycodone sublingually at a dose of 0.1 mg/0.1 mL (pH 4.0 and 9.0). Blood samples were collected at different time points, and plasma oxycodone concentrations were determined by LC/MS. Following administration of a 0.1 mg dose, the average  $C_{\max}$  values were found to be  $64.9 \pm 12.1$  and  $95.2 \pm 10.1$  ng/mL, for pH 4.0 and 9.0, respectively. The area under the curve (AUC) values were found to be 5807.0, and 8965.3 ng.min/mL for formulation pH 4.0 and 9.0, respectively. The mean sublingual bioavailability of oxycodone was  $45.4\% \pm 20.1\%$  and  $70.1\% \pm 17.9\%$ , for pH 4.0 and 9.0, respectively. The formulation pH had no significant influence on oxycodone bioavailability ( $P < .05$ ). A sublingual spray dosage form of oxycodone hydrochloride would be a good alternative for fast onset pain management, especially in children.

**KEYWORDS:** oxycodone, sublingual, spray, acute pain, rabbit.

### INTRODUCTION

Oxycodone (4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-5 $\alpha$ -morphinan-6-one) (Figure 1) is a semisynthetic opioid derived from thebaine<sup>1</sup> that has been in clinical use since 1917.<sup>2</sup> The usual indications for oxycodone are severe acute postoperative or posttraumatic pain and cancer pain.<sup>3</sup>

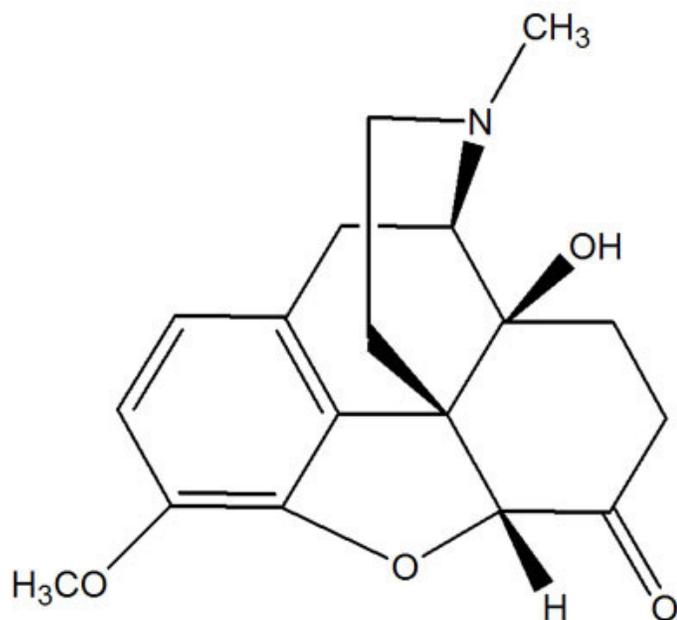
In the United States, oxycodone is available exclusively as oral formulations.<sup>4</sup> In some cases, however, the oral route might not be the best choice for the patient, owing to difficulties with swallowing, or when a faster onset of action is required. Furthermore, parenteral administration may not offer a suitable alternative, owing to decreased venous access. In recent years a growing interest in alternative dosage forms for drug administration has emerged. Accordingly, other novel routes of drug administration have been investigated. In this respect, oxycodone has been administered to humans intramuscularly,<sup>5</sup> intranasally,<sup>6</sup> orally using immediate release solutions or as tablets and controlled-release tablets,<sup>7-9</sup> subcutaneously,<sup>10</sup> and rectally.<sup>11</sup> The rectal administration may result in greater variability compared with oral administration, and while the transdermal route may result in minimal pre-systemic hepatic elimination, it may exhibit a slow onset of action.

Drug delivery via the oral mucous membranes is considered to be a promising alternative to the oral route. In terms of permeability, the sublingual area of the oral cavity (ie, the floor of the mouth) is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (roof of the mouth) area.<sup>12</sup> These differences in permeability are generally based on the relative thickness, the blood supply, and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucous membranes, the extent of drug delivery is also affected by the physicochemical properties of the drug to be delivered. The sublingual route (physiological pH ~6.5)<sup>13</sup> has the potential for providing an alternative to intravenous dosing for rapid delivery of drugs to the systemic circulation. Sublingual drug delivery bypasses gastrointestinal and hepatic presystemic elimination and is an acceptable form of drug delivery applicable in patients with swallowing problems. Furthermore, the high potency of oxycodone makes it suitable for sublingual delivery, owing to limitation in the dose that can be administered. Also, sublingual drug administration is simple and relatively cost-effective.

The purpose of this study was to develop a sublingual spray drug delivery formulation of oxycodone for acute pain management, using rabbit as the animal model, and to evaluate the effect of formulation pH on the sublingual absorption of oxycodone.

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**Figure 1.** Structure of oxycodone (4,5-epoxy-14-hydroxy-3-methoxy-17-methyl-5 $\alpha$ -morphinan-6-one).

## MATERIALS AND METHODS

### Materials

Oxycodone hydrochloride, ethanol, propylene glycol, citric acid, dibasic sodium phosphate, and formic acid were obtained from Sigma-Aldrich Chemical Co (St Louis, MO). Hydrochloric acid, purified water, *United States Pharmacopeia (USP)* chloroform, and high-performance liquid chromatography (HPLC)-grade acetonitrile were obtained from Fisher Scientific (Pittsburgh, PA). Water for HPLC use was passed through a reverse osmosis system (Milli-Q Reagent Water System, Millipore, Billerica, MA) before use. Isoflourane gas for anesthesia was provided by VMC Anesthesia (Ohmeda, Waukesha, WI). Siliconized microcentrifuge tubes, vials, and tips were purchased from Fisher Scientific (Fair Lawn, NJ). Saline (0.9%, injectable) was purchased from Baxter Healthcare Corporation (Deerfield, IL). Heparinized caraway capillary tubes were purchased from Baxter Healthcare Corporation (McGraw Park, IL). Tuberculin slip tip sterile catheters were purchased from J&J Medical (New Brunswick, NJ).

### Animals

Male New Zealand albino rabbits weighing between 3.0 and 3.5 kg (Myrtle's Rabbitry Inc, Thompson Station, TN) were used. The animal work was conducted at the University of Kentucky Chandler Medical Center, Division of Laboratory Animal Resources (DLAR). All research and testing activities related to this work were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) prior to the initiation of this research, and during its execution.

### In Vivo Sublingual and Intravenous Studies

Following introduction of anesthesia (isoflourane general anesthetic gas), a catheter was placed in the marginal ear vein of the rabbit for blood sample collection. For sublingual spray administration, the oxycodone dose (100  $\mu$ g) of either formulation solution 1 (pH 4) or 2 (pH 9) (Table 1) was applied to the sublingual mucosa of the rabbit through a spray bottle (n = 3 rabbits/formulation per route). A separate in vitro spray weight evaluation was performed for the spray bottle before dosing. The spray bottle was hand filled with 2.5 mL deionized water and actuated 10 times for priming before obtaining spray weight data. After priming, net spray weight measurements were taken for 10 consecutive actuations. Target delivery weight for each single spray was ~0.1 g. For intravenous administration, oxycodone hydrochloride aqueous solution was used; a sterile drug solution was prepared by filtration (double 0.22  $\mu$ m filters), and a dose of 100  $\mu$ g oxycodone injected into the marginal ear vein cannula followed by a 0.1-mL flush with 10% (vol/vol) heparin/normal saline solution, to keep the cannula patent.

Aliquot parts of 1-mL blood samples were collected as follows: at baseline, before oxycodone administration; immediately after oxycodone administration; and subsequently at 5, 10, 20, 45, 60, and 120 minutes following oxycodone administration. Blood samples were injected into preheparinized tubes and immediately placed on ice. Plasma was separated by centrifugation at 770 g for 10 minutes, placed in polypropylene tubes, and frozen at  $-20^{\circ}\text{C}$  until the time of analysis.

**Table 1.** Active and Inactive Contents of Formulation Solution 1 (pH 4) and Formulation Solution 2 (pH 9)\*

Active Ingredient/Excipient	Quantity/100 mL	
	Formulation 1 (pH 4.0)	Formulation 2 (pH 9.0)
Oxycodone HCl	100 mg	100 mg
Absolute alcohol	30 mL	35 mL
Propylene glycol	8 mL	8 mL
Phosphate/Citrate buffer	100.0 qs	100.0 qs

\*qs indicates sufficient quantity to make 100 mL.

### Sample Preparation

Protein in rabbit plasma samples was precipitated with 600  $\mu$ L acetonitrile, in 1.5-mL polypropylene test tubes. The samples were vortexed for 20 seconds and centrifuged at 15 330 g for 10 minutes. Five-hundred-microliter aliquot parts of the resulting supernatant were directly transferred to autosampler vials containing low-volume inserts, evaporated to dryness with nitrogen gas at ambient temperature, and then reconstituted with 100  $\mu$ L acetonitrile. Fifty-microliter aliquot parts of this final solution were injected onto the HPLC-MS system.

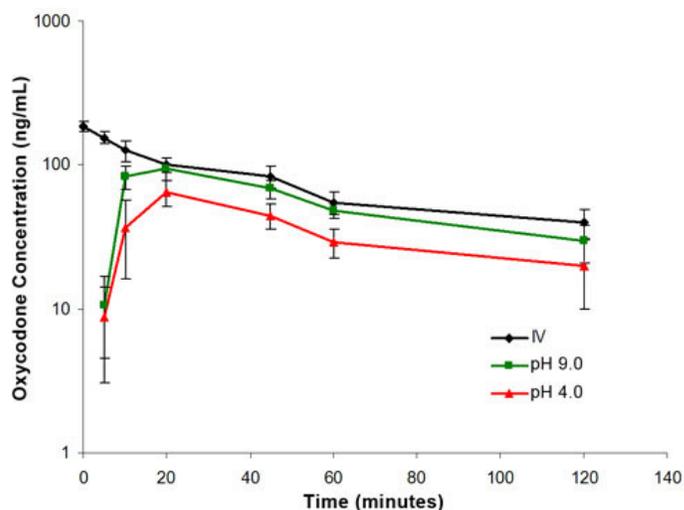
### HPLC-MS Analysis

Chromatography was performed on an Agilent Zorbax Eclipse C<sub>8</sub> (Palo Alto, CA)(4.6 mm  $\times$  150 mm, 5  $\mu$ m) column with a mobile phase consisting of mobile phases (A) water with 0.1% formic acid, and (B) acetonitrile with gradient elution (Table 2). The flow-rate was set at 0.5 mL/min. The LC-MS system consisted of a Waters 2690 HPLC pump (Waters, Milford, MA), a Waters 2695 autosampler (Waters), and a Micromass ZQ detector (Waters), which used electrospray ionization (ESI). Selected ion monitoring (SIM) was performed in the positive mode for oxycodone, M<sup>+</sup> = 316 mass to charge ration (m/z) (dwell time 0.3 seconds); the capillary voltage was 4.5 kV and the cone voltage was 30 V. The source block and desolvation temperatures were 120°C and 250°C, respectively. Nitrogen was used as the nebulization and drying gas at flow rates of 50 and 450 L/h, respectively. Calibration curves were constructed using a linear regression of the drug peak area versus nominal drug concentrations. The method was validated over the concentration range used and found to be satisfactory for the determination of oxycodone in rabbit plasma over the concentration range of 5 to 200 ng/mL. The limit of quantification (LOQ) was established at 5 ng/mL. MS control and spectral processing were performed using MassLynx software, Version 3.5 (Waters).

**Table 2.** Gradient Elution Time-Table Program in the HPLC-MS System Using Mobile Phase A (water with 0.1% formic acid) and Mobile Phase B (acetonitrile)\*

Time (minutes)	A%	B%
0.0	100.0	0.0
2.0	100.0	0.0
15.0	0.0	100.0
18.0	0.0	100.0
20.0	100.0	0.0
22.0	100.0	0.0

\*HPLC-MS indicates high-performance liquid chromatography-mass spectrometry.



**Figure 2.** Mean plasma oxycodone levels following sublingual administration of formulation 1 (pH 4.0), formulation 2 (pH 9.0), and IV administration at 100  $\mu$ g oxycodone hydrochloride dose (n = 3). All values show the mean  $\pm$  SEM.

### Pharmacokinetic Analysis

Concentration-time profiles of oxycodone after intravenous (IV) and sublingual administration of formulations 1 and 2 were evaluated by a noncompartmental model (WinNonlin Professional, Version 4.1, Pharsight Corp., Mountain View, CA). The pharmacokinetic parameters, such as terminal elimination half life ( $t_{1/2}$ ) and AUC from 0 to infinity ( $AUC_{0-\infty}$ ) were estimated using this software.

After a single dose, maximum plasma concentration ( $C_{max}$ ), and time to reach maximum concentration ( $T_{max}$ ) were also determined. The absolute bioavailability of the sublingual formulation was calculated by Equation 1<sup>1</sup>:

$$F = \frac{AUC_{SL}}{AUC_{IV}} \times \frac{Dose_{IV}}{Dose_{SL}} \times 100 \quad (1)$$

where F is the percentage absolute bioavailability, and  $AUC_{SL}$ ,  $AUC_{IV}$ ,  $Dose_{IV}$ , and  $Dose_{SL}$  are the AUC and corresponding dose for the sublingual and intravenous administrations, respectively.

## RESULTS

Figure 2 illustrates the mean plasma oxycodone concentration versus time relationship that resulted after oxycodone formulations 1 and 2 were sprayed onto the sublingual mucosa of the rabbit, in comparison to IV administration of oxycodone. The concentration-time profiles were analyzed by a noncompartmental method, and the pharmacokinetic parameters were determined. The mean AUC values for oxycodone after IV and after sublingual spray delivery of formulations 1 and 2 administration were 12 791 ng.min/mL,

5807 ng.min/mL, and 8965.3 ng.min/mL, respectively. The pharmacokinetic parameters of the 2 formulations in comparison with the IV route are presented in (Table 3).

Following sublingual spray administration, the bioavailability of formulation 1 and formulation 2 were obtained by comparing the mean AUC after intravenous and sublingual administration and were found to be  $45.4\% \pm 20.1\%$ , and  $70.1\% \pm 17.9\%$ , respectively (Figure 2). Two-tailed *t* test analyses indicated that there was no significant difference in oxycodone sublingual bioavailability between the 2 different pH formulations ( $P < .05$ ). In all sublingual studies regardless of formulation pH,  $t_{\max}$  occurred around 20 minutes of spray solution application to the rabbit sublingual mucosa (Figure 2).

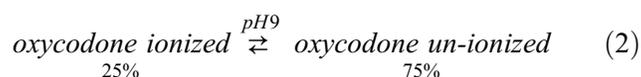
## DISCUSSION

The major emphasis of this work is on the development of a sublingual spray drug delivery formulation of oxycodone for acute pain management. The evaluation of the effect of formulation pH on sublingual absorption of oxycodone was a secondary focus. Spraying the drug formulation directly onto the sublingual mucosa could be a useful delivery system for oxycodone, especially for children. A rabbit animal model was used to investigate sublingual oxycodone absorption because the histology and drug transport properties of rabbit's sublingual mucosa are similar to those of human.

In our present sublingual study with oxycodone, we obtained acceptable times in reaching maximum plasma concentrations (20 minutes) when compared with immediate release oral tablets (1.3 hours), intramuscular (1 hour), and intranasal oxycodone (0.42 hour) in healthy volunteers.<sup>2</sup> The short sublingual  $t_{\max}$  value, which is similar to that obtained after nasal administration, might be the result of a reduction in dose swallowing (ie, reduction of gastrointestinal absorption) by introduction of the dose as a formulated solution through a spray pump device designed to deliver a 0.1-mL dose of the drug. The small droplet size

increases the surface area of contact with the mucosal membrane, thus enhancing drug absorption profiles.<sup>14</sup> Furthermore, Katz and Barr<sup>15</sup> have reported that a formulation solution with an alcoholic component is expected to alter the sublingual absorption profile of a drug, and that the use of the free base or the salt form of a drug with a specific vehicle had a more important effect on sublingual absorption than in oral or subcutaneous delivery.

The characteristics of sublingual absorption of drugs are dependent on both pH and lipid solubility.<sup>16,17</sup> In theory, sublingual bioavailability and absorption could be improved by converting the ionized form of oxycodone to the unionized form (free base) by adjusting the formulation pH. Therefore, it was hypothesized that a low degree of ionization might favor maximal absorption. The analgesic, oxycodone, is a weak base ( $pK_a = 8.53$ ), with a partition coefficient equal to 0.7.<sup>2</sup> Applying the Henderson-Hasselbalch equation, the predominant species in the formulation at pH 9.0 (formula 2) will be the un-ionized oxycodone free base, which will exist in equilibrium with its protonated form (Equation 2), whereas the protonated oxycodone species will be the more predominant form in the formulation at pH 4.0 (formula 1). In this respect, an increase in oxycodone bioavailability was observed with formulation 2 (pH 9.0) compared with formulation 1 (pH 4.0); however, the difference observed was not statistically significant ( $P < .05$ ). Thus, it is hypothesized that the very low lipid solubility of both ionized and unionized oxycodone is the factor contributing most to the limited increase in bioavailability. Other factors that may be contributory are the low dose volume and the weak buffer capacity of the formulations once they are applied to the sublingual mucosal membranes.



In adults, the bioavailability of oral, nasal, and rectal oxycodone has been reported to be 40% to 60% when compared with parenteral administration.<sup>6,11</sup> Buccal and intranasal administration of oxycodone hydrochloride both afford similar bioavailability of around 55%.<sup>6,18</sup> This finding is in close agreement with the sublingual bioavailability of  $45.4\% \pm 20.1\%$  obtained in this study. More important, the bioavailability of oxycodone was increased to  $70.1\% \pm 17.9\%$ , when the formulation pH rose up to 9.0; however, this difference in bioavailability was found to be statistically insignificant ( $P < .05$ ).

The terminal half-life of oxycodone after IV administration was close to the terminal half-life after sublingual administration. This result implies that there is no long-term deposition of oxycodone in the sublingual mucosa after transmucosal delivery.

**Table 3.** Pharmacokinetic Parameters Following IV Administration and Sublingual Spray Administration of Formulation 1 (pH 4.0) and Formulation 2 (pH 9.0) to Rabbits (n = 3)\*

Parameter Average and Unit	IV	Sublingual (pH 4.0)	Sublingual (pH 9.0)
$C_{\max}$ (ng/mL)	185.0	64.88	95.24
$t_{\max}$ (hours)	0	0.33	0.33
$t_{1/2}$ (hours)	1.13	1.00	1.11
$AUC_{\infty}$ (ng.min/mL)	12791	5807.0	8965.3
$AUC/AUC_{IV}$	1.00	$0.454 \pm 0.020$	$0.701 \pm 0.179$

\*IV indicates intravenous administration.

Bypassing first-pass metabolism of oxycodone by the gastrointestinal tract and the liver by administering the drug via sublingual spray enhanced oxycodone bioavailability. Also, a sublingual formulation of oxycodone permits the use of lower doses of oxycodone for pain management, since a greater portion of the medication is absorbed directly into the bloodstream, thereby allowing a direct route to the afflicted target area.

## CONCLUSION

A sublingual spray solution dosage form may be an alternative route of administration for oxycodone for providing fast onset of pain relief for acute pain management. The formulation pH appears to have no significant effect on sublingual absorption of the oxycodone spray formulation.

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